Mundschenk et al. (WO 97/43407) merely represents Applicant's own prior teaching of the preparation and use of preferred inactivated bioactive peptides. It should be noted that the "bioactive" peptides described therein include a variety of toxins, and similar peptides, and hence are quite *unlikely* to be delivered to the body at all, or in any form, let alone directly to a surface within the mouth. Clearly nothing in the reference itself teaches or suggests buccal delivery in this manner, let alone using the formulation presently described and claimed.

Nor has the Examiner yet cited any reference that suggests the delivery of an "inactivated bioactive peptide" in the buccal cavity, using any system or approach whatsoever. In fact, Heiber et al. 5,766,620 is merely cited for the mere proposition that "peptides are buccally administratable". The Action ignores the fact, however, that Heiber et al. do not describe the peptides of the present invention, nor do the compositions of Heiber et al. include the use of benzalkonium chloride, particularly in the manner presently claimed.

Nor do Dondeti et al. or Siegel et al. remedy the defects of the previous two references, including those described above.

At its closest, Dondeti et al. merely describes the use of benzalkonium chloride as a *preservative*, and then only *in addition to* the use of 2-phenylethanol as an additional preservative. The effect of both preservatives, in turn, was evaluated *not* to determine their effect (collectively) on delivery, *per se*, but instead in view of the possible effects of such preservatives on "globule size" and on "ciliary beat frequency". These effects, however, are clearly unique to the "microcrystalline cellulose" composition of Dondeti et al., as compared to the present formulation, and to nasal, as compared to buccal, delivery.

Contrary to the suggestion set forth in the current Action, Applicants have not asserted that such effects are unique to the microcrystalline cellulose used in Dondeti. Hence no "supportive data" of such an assertion would appear to be necessary. To the contrary, Applicants do assert, and there can be no dispute, that the results set forth in Dondeti are derived from, and based on, the particular circumstances set forth in that reference, including the use of such cellulose. It is therefore the Examiner's assertion, namely that results derived from such a system are somehow relevant, let alone *suggestive* of Applicant's current invention, that would seem to require supportive data.

Similarly, Siegel et al. investigate the effect of surfactants, including benzalkonium chloride, on the permeability of canine mucosa, using a variety of test molecules. At its *closest*, the reference evaluates the effect of benzalkonium chloride (at concentrations of 0.025%, 0.1% and 1.0%).on the permeability of insulin. Note that only the *lowest* of these concentrations is even within the most preferred enhancer concentration ranges of the present invention (see, page 6, lines 22-27 of the specification). The data at Table I of Siegel et al., however, shows that this concentration fails to provide *any* significant improvement as compared to the control. It is only at significantly higher concentrations (at or well exceeding Applicant's outermost concentration range) that "permeability" is increased. Rather than true permeability, however, the increase at these concentrations would presumably be due, in large part, to the severe disruptive effect the surfactant would be expected to have on membranes.

The current Action expresses confusion regarding the relationship between the concentrations described in Siegel et al. and those of the present invention. Applicants merely maintained that the *preferred* concentrations of the present invention (as set forth in claims 13 and 14) of are well outside of any concentration that provided "permeability" in the experiment of Siegel et al. The Action goes on to assert that the ranges of claims 13-14 include the ranges of Siegel et al., with apparent reference to the 0.025% sample of Siegel et al., yet *ignores* the fact that Siegel showed no apparent increase in "permeability" at all at this level. These distinctions based on concentrations can be combined with others as well, including the fact that Siegel et al. suggests nothing about the use of an inactivated bioactive peptide, or buccal delivery.

The rejection of claims 5 and 51 under Section 103(a) is respectfully traversed. Mundshenk, Dondeti et al. and Siegel et al. are distinguished for the reasons set forth above, and for others as well.

The current Action suggests that it is improper to show nonobviousness by attacking references individually, where the rejections are based on combinations of references. To the contrary, Merely combining such references does not some magically render any such defects moot, or make disparate teachings somehow or suggestive of each other, where they do not otherwise exist.

The Commissioner is hereby authorized to charge any additional filing fees required to Deposit Account No. 061910. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

Dated: 27 AUG 2002

Philip M. Goldman
Registration No. 31,162
Fredrikson & Byron, P.A.
4000 Pillsbury Center
200 South Sixth Street
Minneapolis, MN 55402-1425
(612) 492-7088
Customer No. 022859

::ODMA\PCDOCS\FBDOCS1\2692755\1